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Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices: Draft Guidance

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Webinar Objectives

- To provide an overview and context of the proposed framework;

- To answer clarifying questions about the specific concepts in the draft guidance.

Goal: enable stakeholders to provide better feedback to the dockets

Key Messages

- Despite a recognized need, relatively few medical devices have pediatric-specific indications and labeling.
- The draft guidance proposes a framework to consider leveraging data from adult populations to augment what is known about a device's performance in pediatric patients.
- The approach described in this draft guidance could stimulate growth in the number of devices specifically indicated and labeled for pediatric patients.

Guiding Principles

- The draft guidance does not change the threshold for approval or for valid scientific evidence.

- When existing adult clinical data are relevant and appropriate for leveraging, this may reduce the amount of prospective data in the pediatric population needed to arrive at a reasonable assurance of effectiveness and/or safety (or probable benefits outweigh risks, for HDE). If it is not appropriate, then no data will be leveraged.

- The appropriateness of extrapolation is considered *case by case* following the decision tree, and will be considered separately for effectiveness and safety.

Outline

- Pediatric Device Challenges
- CDRH Definition of Pediatric
- What is extrapolation? Why consider extrapolation?
- Purpose of Guidance & Specific Objectives
- Policy History/ Stakeholder Input
- Overview / Key Guidance Elements
- Why extrapolate device safety data?
- Suggested Decision Process
- Possible Extrapolation Decisions
- Conclusions & Next Steps

Challenges

- Challenges in the development of medical devices labeled for pediatric use.
  - Small and diffusely scattered potential pediatric populations lead to small trial sizes
  - Challenges exist in enrollment and consent procedures, which could increase the length of time needed to determine safety and effectiveness.
  - There are more variations in pathophysiology, physiology, anatomy, and human factors in children and within pediatric subpopulations as compared to adults.
  - Reference samples may require an amount of blood too voluminous to obtain safely from a neonate or small child.

- Challenges in regulation of pediatric devices
  - Extensive off-label use of adult devices without labeling information to promote safe and effective use in pediatric patients.

CDRH Definition of Pediatric

- Age ranges for these pediatric subpopulations are as follows:
- Neonates: from birth through the first 28 days of life
- Infants: 29 days to less than 2 years
- Children: 2 years to less than 12 years
- Adolescents: aged 12 through 21 (up to but not including the 22nd birthday)
- Transitional Pediatrics: aged 18 through 21 years

What is extrapolation?

For the purposes of this document, "extrapolation" refers to the leveraging process whereby an indication for use of a device in a new pediatric patient population can be supported by existing clinical data from a studied patient population.

Why consider extrapolation?

- Stimulate development of and labeling for devices available for treatment of US pediatric patients, while ensuring that the approval of these devices is based on valid scientific evidence
- Promote proper labeling and indications for safer and more effective device use in pediatric patients
- Leverage relevant available clinical evidence to streamline requirements for establishing a pediatric intended use claim

Purpose of Guidance

- To the extent that the existing data are relevant and similar to how the device is expected to perform clinically in the intended pediatric population, we believe those data may be leveraged to bolster other valid scientific evidence including newly collected pediatric data when appropriate.

Objectives of Guidance

1. to increase the availability of safe and effective pediatric devices by leveraging relevant existing clinical data for use in pre-market approval applications (PMAs) and humanitarian device exemptions (HDEs);
2. to explain the circumstances in which FDA believes it may be appropriate to leverage existing clinical data to support pediatric device indications and labeling;
3. to outline the approach FDA uses to determine whether extrapolation is appropriate, and if so, to what extent the data can be leveraged; and
4. to describe statistical methodology that can be used to leverage the data in a way that increases precision for pediatric inferences.

Policy History

- CDRH published a final guidance document in 2004 entitled “Premarket Assessment of Pediatric Medical Devices.” This document indicates that data can be extrapolated to support effectiveness and safety for premarket approval applications (PMAs) when consistent with scientific principles.
- In 2007, Congress passed the Pediatric Medical Device Safety and Improvement Act (PMDSIA), which permits extrapolation of adult effectiveness data to support a pediatric indication if the disease course or the effect of the device in adults is likely to be the same in children.
- Workshop to discuss approach to extrapolation of adult data for pediatric populations. Participants stakeholders and FDA staff. (December 2011)
- CDRH Medical Officer Working group convened to plan approach

Synopsis

- In order to make decisions about the effectiveness and safety of a medical device in pediatric patients, the Food and Drug Administration (FDA) considers the totality of the evidence available.
- The scope of this draft guidance includes medical devices subject to the PMA and HDE premarket requirements.
- This guidance facilitates efforts to address an unmet medical device need for pediatric patients.

Key Guidance Elements

- Permits Extrapolation of Effectiveness and Safety data, where appropriate. Safety and effectiveness are treated *independently* for extrapolation purposes.

- Decision tree outlines how to decide whether or not extrapolation is appropriate

- Appendix with statistical guidance on potential methods for extrapolation, and examples of extrapolation (six hypothetical and one actual example).

Why extrapolate device safety data?

- Existing adult clinical data may provide valid scientific evidence about device safety which is relevant to risks in children.
- Mechanism of action of devices is often expected to be similar in adults and pediatric patients, while dosing and PK issues routinely differ for drugs.
- Other forms of scientific evidence may be used to assess many device performance characteristics related to safe device functioning (e.g., pre-clinical testing, engineering, computer modeling, or other nonclinical data).
- As with any PMA or HDE, FDA will still consider clinical data (whether extrapolated or not) alongside other forms of scientific evidence from assessments of device performance (e.g., preclinical testing, engineering models, biocompatibility, virtual patient simulations, literature studies or case reports), to determine whether the sponsor has demonstrated a reasonable assurance of safety and effectiveness in the intended pediatric population.

Suggested Decision Process

Assess:

- Relevancy of Adult (or other Pediatric Subpopulation) Data
- Expected Similarity of Response to Intervention
  - Device characteristics
  - Disease characteristics
  - Population characteristics
- Data Quality

(Refer to Figure 1 of the draft guidance for complete decision tree)

Possible Extrapolation Decisions

- Extrapolation of adult data may be done in full or partially through statistical modeling.
  - Full extrapolation: existing clinical data are used directly (i.e., as a complete substitute) for prospective pediatric clinical data.
  - Partial extrapolation: existing data are combined via a statistical model with pediatric data sources or prospective pediatric clinical data.
    - Partial extrapolation permits utilization of existing clinical data to support demonstration of device safety or effectiveness for use in pediatric patients, with the expectation that some pediatric data are necessary.
    - The existing clinical data bolster any newly collected pediatric data.
- If not appropriate or insufficient to meet the threshold of valid scientific evidence, data will not be extrapolated.

Concluding Remarks

- Despite a recognized need, relatively few medical devices have pediatric-specific indications and labeling.
- The draft guidance proposes a framework to consider leveraging data from adult populations to augment what is known about a device's performance in pediatric patients.
- The approach described in this draft guidance could stimulate growth in the number of devices specifically indicated and labeled for pediatric patients.

Next Steps

- Finalize draft guidance
  - Consider public comments to the docket
    - Docket Number - FDA-2015-D-1376

- Implementation
  - CDRH will use pediatric expertise in the evaluation of any application suggesting extrapolation

Questions?

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